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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,066	10/19/2001	Michael Hallek	50125/019001	8894

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 06/29/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,066	HALLEK ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 November 2004 and 06 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,11-16 and 29-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,11-16 and 29-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 November 2004* is/are: a)☒ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 11/22/04 and a supplemental amendment field 4/6/05. Claims 2-5, 7-10 and 17-28 have been cancelled. Claims 29-42 have been added. Claims 1 and 11-16 have been amended. Claims 1, 6, 11-16 and 29-42 are pending in the application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Priority

The instant application is a 371 of an International application PCT/EP99/04288, filed 6/21/1999, which claims priority to a foreign application DE 19827457.1. Applicants inserted a specific reference to the earlier filed applications in an amendment filed 2/19/04. As the instant nonprovisional application entered the national stage after compliance with 35 U.S.C. 371 from an international application filed under 35 U.S.C. 363 before November 29, 2000, the specific reference can be inserted at any time.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 11-16 and 29-42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants claim a genus of structural proteins with at least one mutation that is capable of particle formation and results in the increased infectivity of viruses containing the mutated structural protein. **This rejection is maintained for reasons of record in the office action filed 10/16/03 and 5/18/04 and restated here. The rejection has been extended to newly added claims 29-42.**

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

The instantly claimed invention recites a mutated structural protein that is capable of particle formation and increases infectivity of AAV. Applicants teach that the mutation by way of point mutations, mutations of several amino acids, deletion or insertion mutations and combinations of these mutations ultimately alter cell-targeting specificity with increased infectivity. Specifically, the specification teaches insertion of a laminin P1 ligand into VP1 and VP3 (pages 16-20). One viral particle that results from insertion of P1 into amino acid 587 (I-

587) is shown to have increased infectivity of M07-LP1-R and B16F10 cells. It is also mentioned that VP3 protein was mutated by the insertion of Z34C domain of protein A but no indication about the ability of the structural protein to form particles or increase infectivity is provided. The disclosure of insertion of the P1 ligand at amino acid 587 to alter specificity to the two cell types is not accompanied by a disclosure as to the relative properties or a correlation between structure of this mutation and its ability to alter infectivity. Therefore, there is no clear description of the structural or functional characteristics required for any other mutations to increase infectivity. Given the large number of mutations envisioned by the invention and the diversity of the cellular receptors and ligands encompassed by the claims and the inability to determine which mutation will increase infectivity, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of one species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus.

Response to Arguments-35 USC § 112, first paragraph

Applicants traverse the rejections under 35 U.S.C 112, first paragraph on pages 15-19 of the amendment filed 11/22/04. Applicants argue the claims require very "specific structural characteristics". For claim 1, the mutation is surface-located and at the N-terminus of the protein. For claims 11-16, the mutation contains an insertion or deletion in very specific locations of the VP-1 protein. Additionally, very specific functional characteristics are required of the proteins that the mutations result in an increase in infectivity. Applicants further take issue to the rejection of claims 11-16 which are particular mutations and are not appropriately broad genus of

mutations. Similarly, applicants argue that claim 1 structurally is limited to mutations in the N-terminus. Thus using sound scientific reasoning, the sites of mutations in all of these protein was selected. Applicants also argue that several experimental results (described in detail below) demonstrate that the specification teaches a general strategy for producing structural proteins that facilitate increased viral infectivity.

Applicant's arguments filed 11/22/04 have been fully considered but they are not persuasive. Claim 1 broadly recites any AAV serotype and any structural protein that comprises a mutation. Functionally, the mutated structural protein is capable of particle formation and the mutation brings about an increase in the infectivity of AAV. Structurally, the mutation is in the surface located region **or** the N-terminus of the structural protein. This is a broad genus of mutant structural proteins. Claims 11-16 recites a structural protein from any AAV serotype distinguished by specific cleavage sites. The claims do not specify a specific AAV with these cleavage sites but any AAV with these cleavage sites. Applicants have not demonstrated that they were in possession of this broad class of proteins. Furthermore, the specification discloses a single example of structural mutants, which comprise insertions that have increased infectivity and can also form particles. As demonstrated in table 3, insertion at amino acid 587 results in increased infectivity in B16F10 cells.

As to the experimental results that demonstrate that the specification teaches a general strategy for producing structural proteins that facilitate increased viral infectivity, the following arguments are provided.

1) Applicants argue that Tables 1 and 2 demonstrate that a variety of insertions in either VP1 or VP3 support viral particle formation. This argument is not found persuasive because,

Tables 1 and 2 depict five insertion mutants. Of these insertions, only one can tolerate the mutation and form particles and have increased infectivity. This mutant is at site 587.

2) Applicants argue that on page 28 they described several VP3 insertions with Z34C and as demonstrated by Reid et al the Z34C mutant is retargeted and thus has increased infectivity. This argument is not found persuasive because only a single insertion is demonstrated by Reid to retarget AAV particles. The insertion is following amino acid 587.

3) Applicants argue that Nicklin et al demonstrate that ligands other than P1 can be inserted into AAV and result in viral particle formation with retargeted infectivity. This argument is not found persuasive because the rejection is not based upon the written description of the actual ligand inserted into the vector. Rather the rejection is based upon the lack of written disclosure over means of identifying sites of mutation. Applicants' claims are drawn to a broad class of mutant structural proteins in which the mutation is in a surface located region or the N-terminus. However, following the guidance in the specification only a single site of insertion has been identified and that is at 587. Furthermore, Nicklin et al only demonstrate that insertion of a peptide at I-587 with a resultant AAV particle with altered tropism.

4) Applicants argue that Grifman et al demonstrate that ligands other than P1 can be inserted into AAV and result in viral particle formation with retargeted infectivity. Specifically, applicants point to Grifman which teaches that insertion after one of the amino acids in SEQ ID NO:7 as recited in claim 14 leads to altered tropism. This argument is not found persuasive because the insertion demonstrated to be effective at retargeting AAV vectors in Figure 6 is an insertion following amino acid 587. Again, this is the same mutation that applicants have demonstrated is capable of tolerating insertions. Furthermore as argued above, it is not the

nature of the ligand that is at question but the lack of guidance in the specification as to the site of mutation such that the mutated structural protein can form an infectious particle that has increased infectivity.

5) Applicants argue that Wu et al describes six mutants capable of presenting foreign epitopes or ligands for AAV retargeting to alternative receptors. Specifically, applicants point to aa266 and aa591, which correspond to insertions at SEQ ID NO:2 and SEQ ID NO:7. This argument is not found persuasive because Wu et al teach that insertions at aa266 and aa591 result in decreased infectivity by 2-3 logs (see e.g. table 5). Wu et al teach that the insertions sites have the potential for altered tropism. Therefore, Wu et al do not teach that the resultant AAV particles have increased infectivity. Furthermore, any differences between the teachings of Wu et al and the instant specification must be considered as inventive experimentation. Wu et al do not utilize the methods of the instant specification to identify the sites of insertion. Rather, Wu et al generates 93 mutants at 59 locations. The sites were mutated by insertion of epitopes or ligands, by alanine-scanning mutagenesis in which 2-5 amino acids are altered to alanine residues and epitope substitution mutations. Therefore, applicants generated a functional map of the AAV2 capsid and demonstrated which sites could actually tolerate substitutions, deletions or insertions. Ultimately, Wu et al identify six sites that have the potential to tolerate insertions. Of these aa34 and aa138 were assayed *in vitro* for and demonstrated altered tropisms. By contrast, the instant specification suggests identifying surface located regions by either comparison of sequences of several AAV serotypes or computer assisted comparison of CPV, AAV2 and B19. In the instant specification, a single site is demonstrated to have the functional characteristics recited in the claims. The art except for Wu et al does not advance this characterization for

reasons stated above. However, Wu et al constitute an inventive experimental step that does not support the written description provided in the instant specification. Therefore, the skilled artisan cannot envision the detailed structure of the broad class of recited AAV mutant structural proteins regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that the protein is part of the invention and a reference to a potential method for isolating it. The disclosure of a single member of this genus does not suggest that the applicant was in possession of the genus.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 6 and 31-42 are rejected under 35 U.S.C. 102(a) as being anticipated by Mamounas et al WO 97/38723 publication date October 23, 1997 (provided by applicant), see entire document. **This rejection is maintained for reasons of record in the office action filed 10/16/03 and restated here. The rejection has been slightly reworded based upon applicants' amendments and has been extended to newly added claims 31-42.**

Mamounas et al teach at least one mutation in an AAV structural protein . The mutated structural protein is capable of particle formation in a triple co-transfection method and the resulting particle has an increase in infectivity. The mutation is located at the N-terminus of AAV2 VP-1, VP-2 or VP-3 (see e.g. page 61, line 33-35, page 67, line 24-26, page 69, line 11-

14 and line 15-26 and table 3) as recited in claims 1, 6 and 33. Mutations include insertions and deletions and substitutions (see e.g. page 20, line 4-15) as recited in claim 34. The resultant particles bind to selected cell types (see e.g. page 4, line 21-31) and binding at the wild-type receptor 150 kD heparan sulphate proteoglycan receptor is reduced (see e.g. page 3, line 9-15) as recited in claims 31 and 32. Envisioned targeting molecules include targeting peptides or proteins such as C4 peptide or monoclonal antibody single chain fragments (see e.g. page 17, line 30 through page 19, line 10). For example, VP-1, VP-2 and VP-3 were incorporated with C4 at their N-terminus (see e.g. page 43, line 28-30) or were mutated to incorporate a single-chain fragment variable region of a monoclonal antibody against the CD34 molecule (sFv) at their N-terminus (see e.g. page 67, line 24-26) as recited in claims 35 and 36. Nucleic acid comprising the structural protein is used to generate rAAV within HeLa and is part of the capsid and hence part of the particle (see e.g. page 68, line 19-31) as recited in claims 37-41. The resultant particle has altered tropism (see e.g. page 69, line 15-26) as recited in claim 42.

Response to Arguments-35 USC § 102

Applicants traverse the rejection of claims under 35 U.S.C 102(a) as anticipated by Mamounas et al on pages 11-15 of the amendment filed 11/22/04. Applicants' argue the following. 1) Mamounas does not teach that the rAAV chimeric virion " is capable of particle formation" as required in the instant claims. Applicants argue that Mamounas teaches that following failure to produce viral particles, the transfection system had to be modified to include wild-type capsid proteins. Mamounas is in contrast to the instant invention that teaches that the structural proteins are responsible for increased infectivity and particle formation. 2) Applicants

present arguments as to why the prior art does not read on claims 11-16. these arguments are moot as these claims have not been rejected as anticipated by Mamounas.

Applicants' arguments filed 11/22/04 have been fully considered but they are not persuasive. While claim 1 has been rejected as anticipated by Mamounas, claims 11-16 are not included in this rejection. Applicants have argued that Mamounas does not teach that the rAAV is capable of forming particles. However, as taught in Table 3 and on page 69, line 11-14 and line 15-26, rAAV particles were generated using the mutated structural proteins. And these particles had an increase in infectivity. Applicants appear to argue that the inclusion of a plasmid comprising wild-type capsid means that the methods of Mamounas et al include steps that are not recited in the instant claims which occludes it use as prior art. By this argument, it is taken to mean that the particle is only formed from mutated structural protein, However, during prosecution, claims must be interpreted as broadly as their terms reasonably allow. The broad interpretation that can be afforded "the mutated structural protein is capable of particle formation" is that the mutated structural protein can be involved in particle formation and is thus a part of the final particle and capsid. The specification teaches formation of a particle and a capsid that is a mix of wild type and mutated structural proteins such as in the instance of formation of a particle comprised of P1 inserted into VP-3 yet VP-1 and VP-2 are wild-type. Therefore, the formation of particles that are part wild type and part mutated is not occluded by the instantly recited claims nor does the specification teach that only mutated proteins are part of the capsid.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

June 15, 2005

JAMES KETTER
PRIMARY EXAMINER